PATENT SPECIFICATION

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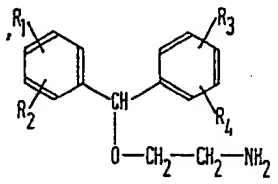
(54) DIPHENYLMETHOXYETHYLAMINES

(71) We, GIST-BROCADES N.V., a Dutch Body Corporate of Wateringseweg 1, Delft, Holland, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to therapeutically useful basic ethers and acid addition salts thereof, to processes for their preparation and to pharmaceutical compositions containing them.

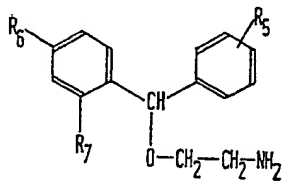
The ethers with which the present invention is concerned are substituted diphenylmethoxyethylamines. Compounds of this type are known, for example from British Patent Specification No. 1219609, French Patent Specification No. 1377277 and United States Patent Specification No. 3032556. Said patent specifications disclose compounds encompassed by the general formula:



I

in which the symbols R_1, R_2, R_3 and R_4 are the same or different and each represents a hydrogen or halogen atom or a lower alkyl group. The ethers of general formula I have been disclosed as being useful only as intermediates for therapeutically useful compounds.

It has now unexpectedly been found after research and experimentation that a certain class of ethers within general formula I and conforming to the general formula:



II

in which R_5 represents a fluorine, bromine or chlorine atom, R_6 represents a hydrogen or fluorine atom and R_7 represents a hydrogen, fluorine or chlorine atom, with the provisos that R_7 is a hydrogen atom when R_6 is a fluorine atom and R_5 is a fluorine atom when R_7 is a chlorine atom, and acid addition salts thereof, possess therapeutic properties in their own right.

The ethers of formula II except for the compound in which R_5 represents a chlorine atom and R_6 and R_7 represent hydrogen atoms, i.e. 2 - {[α - (p - chlorophenyl)-benzyl]oxy}ethylamine, which is disclosed in Example XXIV of United States Patent Specification No. 3032556, are new compounds and as such they and acid additional salts thereof constitute the most important feature of the invention.

The ethers of formula II show valuable biological activities, indicating that the compounds have dopaminergic properties. The compounds induced so-called bizarre social behaviour in rats (A. J. J. C. Lammers and J. M. van Rossum, Eur. J. Pharmacol, 5, 103—106 (1968)). They possess reserpine and α - methyl - p - tyrosine antagonizing properties and they cause turning behaviour in rats with one-sided striatal lesions (N. E.

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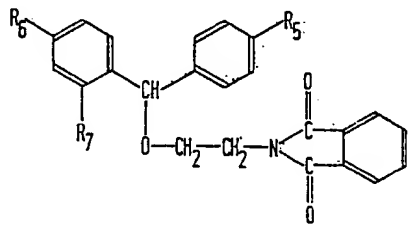
Anders *et al.*, Acta Pharmacol. et Toxicol., 24, 263—274 (1966)). The haloperiodol-induced catalepsis, which is of dopaminergic origin, is more strongly antagonized than the catalepsis caused by chlorpromazine, which is of a more adrenergic type. These activities are typical for compounds like L-Dopa and apomorphine. The ethers of formula II, however, do not cause vomiting when administered to dogs. The ethers of formula II are therefore useful agents in combatting Parkinson's disease.

The most active—and therefore preferred—ethers are those of formula II in which R_5 represents a fluorine or chlorine atom and R_6 or R_7 represents a fluorine atom, and particularly the compounds 2 - [bis(*p* - fluorophenyl)methoxy]ethylamine, 2 - {[*p* - chloro - α - (*p* - fluorophenyl)-benzyl]oxy}ethylamine and 2 - {[*o* - fluoro - α - (*p* - fluorophenyl)benzyl]oxy}ethylamine and their acid addition salts.

For use as therapeutics the ethers of formula II may be used as bases or as acid addition salts containing pharmaceutically acceptable non-toxic anions, e.g. the hydrohalides, sulphates, oxalates, tartrates, fumarates, citrates, maleates, succinates and lactates.

The bases or non-toxic acid addition salts thereof may be administered orally or parenterally in a pharmacologically acceptable carrier according to accepted pharmaceutical practice. In adults the oral dosage will be from 10 to 100 mg. daily.

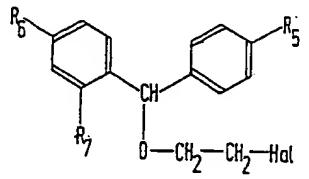
According to a feature of the invention, the new ethers of formula II are prepared by removing by a method known *per se* the phthaloyl group from a phthalimide derivative of the general formula:



III

in which the R symbols are as hereinbefore defined, to leave an amino radical. Preferably the phthalimide derivative is reacted with hydroxylamine or an acid addition salt thereof, as room temperature in the presence of an alkoxide, such as sodium methoxide, dissolved in a lower alcohol, such as methanol or ethanol.

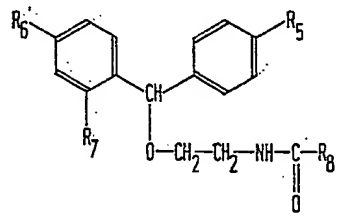
The starting materials of formula III may be prepared by reacting an ether of the general formula:



IV

in which Hal represents a halogen atom and the R symbols are as hereinbefore defined, with potassium phthalimide, preferably by refluxing the reactants in a polar solvent capable of dissolving potassium phthalimide, such as dimethylformamide.

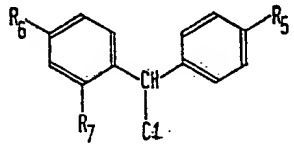
According to another feature of the invention, the new ethers of formula II are prepared by hydrolyzing an amide of the general formula:



V

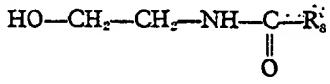
in which R_8 represents a hydrogen atom, or an alkyl, aryl or aralkyl group, said groups containing at most 10 carbon atoms, and R_5, R_6 and R_7 are as hereinbefore defined. The reaction is preferably carried out by refluxing the amide in a lower alcohol, such as ethanol, with a base such as sodium hydroxide.

The starting materials of formula V may be prepared by reacting a substituted diphenylmethyl chloride of the general formula:



VI

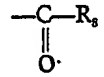
in which the R symbols are as hereinbefore defined, with a compound of the general formula:



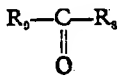
VII

in which R_8 is as hereinbefore defined. The reaction is preferably carried out by refluxing the reactants in an inert organic solvent, such as benzene or toluene, in the presence of a base, such as potassium carbonate or a tertiary amine (e.g. triethylamine).

The compounds of formula VII may be obtained by replacing a hydrogen atom of the amino group in aminoethanol by a group



by a method known *per se* for the acylation of primary amines. The aminoethanol may, for example, be reacted with an ester or acid halide of the general formula:

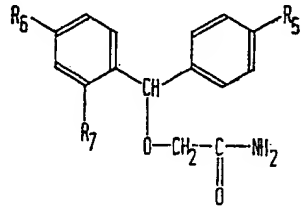


VIII

in which R_9 represents a halogen atom or a lower atom or a lower alkoxy group, and R_8 is as hereinbefore defined. The reaction may be carried out by refluxing a mixture of the reactants if necessary dissolved in an inert organic solvent such as benzene or toluene.

According to another feature of the invention, the new ethers of formula II are prepared by reacting an ether of formula IV with ammonia. The reaction is preferably carried out by heating in a closed vessel the compound of formula IV, dissolved in a lower alcohol (e.g. methanol), with a large excess of ammonia.

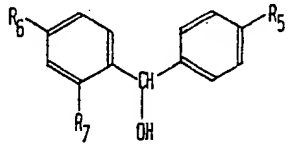
According to another feature of the invention, the new ethers of formula II are prepared by reducing by a method known *per se* an amide of the general formula:



IX

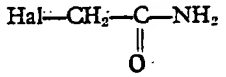
in which the R symbols are as hereinbefore defined. The reduction is preferably effected by reaction of the amide, preferably dissolved in diethyl ether or tetrahydrofuran, with lithium aluminium hydride, followed by decomposition of the complex compound obtained with water.

The starting materials of formula IX may be prepared by reacting a substituted benzhydrol of the general formula:



X

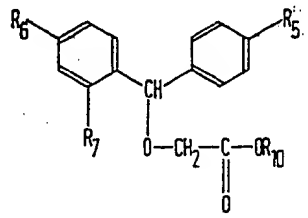
in which the R symbols are as hereinbefore defined, with a compound of the formula:



XI

in which Hal is as hereinbefore defined, preferably by heating the reactants in an inert organic solvent, such as benzene or toluene, in the presence of a base, such as sodium carbonate or a tertiary amine (e.g. triethylamine).

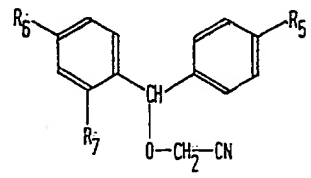
The amides of formula IX may also be prepared by reacting an ester of the general formula:



XII

in which R_{10} represents a lower alkyl group and R_5, R_6 and R_7 are as hereinbefore defined, with ammonia. The ester may, for example, be kept standing for a considerable time (e.g. 10 to 20 hours) with an excess of ammonia, dissolving in a lower alcohol such as methanol.

According to another feature of the invention, the ethers of formula II are prepared by reducing a nitrile of the general formula:



XIII

in which R_5, R_6 and R_7 are as hereinbefore defined, by a method known *per se* for the reduction of a nitrile to a primary amine.

The reduction is preferably carried out by refluxing the nitrile in an organic solvent, such as diethyl ether or tetrahydrofuran, with lithium aluminium hydride, followed by decomposition of the complex compound obtained with water.

The starting materials of formula XIII may be prepared by reacting a diphenylmethyl chloride of formula VI with hydroxyacetonitrile, preferably by refluxing the reactants in an inert organic solvent (e.g. benzene or xylene) in the presence of a base, such as sodium carbonate or triethylamine.

The starting materials of formula XIII may also be obtained by dehydrating an amide of formula IX, for example by refluxing the amide in an inert organic solvent such as toluene or xylene with phosphorus pentoxide.

Acid addition salts of the ethers of formula II may be prepared by methods known *per se*. For example, the base may be treated with the equivalent amount of the acid in an inert organic solvent, such as diethyl ether.

By the term "methods known *per se*" as used in the specification is meant methods heretofore used or described in the literature.

The qualification "lower" as applied in this specification to alcohols and alkoxy and alkyl groups means that the alcohol or alkoxy or alkyl group contains at most 6 carbon atoms.

The following Examples illustrate the preparation of ethers of general formula II by aforementioned processes of the present invention.

EXAMPLE 1

A mixture of 28.2 g. (0.1 mole) of 2 - [bis(*p* - fluorophenyl)methoxy]ethyl chloride and 17 g. (1 mole) of ammonia in 187.5 ml. of methanol is shaken in an autoclave for a period of 6 hours at 135°C. The reaction mixture is poured into water and extracted with diethyl ether. The extract is acidified with 2N hydrochloric acid. The acid aqueous layer is separated off, made alkaline with 2N sodium hydroxide and extracted with diethyl ether. The extract is dried over potassium carbonate and the ether is distilled off. The residue is distilled, yielding 15.4 g. of 2 - [bis(*p* - fluorophenyl)methoxy]ethylamine, boiling point 130°C./0.2 mm.Hg. The base is dissolved in diethyl ether and an ethereal solution of maleic acid is added. The precipitate is filtered off and crystallised from a mixture of ethanol and diethyl ether. 2 - [Bis(*p* - fluorophenyl)methoxy]ethylamine hydrogen maleate is obtained. Its melting point is 126—127°C.

EXAMPLE 2

A solution of 16.1 g. (0.057 mole) of 2 - [bis(*p* - fluorophenyl)methoxy]ethyl chloride and 10.5 g. (0.057 mole) of potassium phthalimide in 55 ml. of dimethylformamide is refluxed for 2 hours. The mixture is cooled and water is added. The aqueous layer is extracted with toluene and the extract is dried over potassium carbonate and concentrated by evaporation of solvent. The residue consists of *N* - {2 - [bis(*p* - fluorophenyl)methoxy]ethyl}phthalimide, m.p. 109.6—111°C.

A solution of 12.5 g. (0.18 mole) of hydroxylamine hydrochloride in 180 ml. of ethanol is added to 90 ml. of 4N sodium methoxide. The sodium chloride formed is filtered off and a solution of 22 g. (0.056 mole) of the aforesaid phthalimide derived in 120 ml. of ethanol is added. The mixture is stirred for 30 minutes. The alcohol is distilled off and the residue is shaken with with diethyl ether and water. The ethereal phase is separated off, dried over potassium carbonate and concentrated by evaporation of solvent. The residue is distilled, yielding 2 - [bis(*p* - fluorophenyl)methoxy]ethylamine, boiling point 120—126°C./0.15 mm.Hg. The base is dissolved in diethyl ether and ethereal hydrogen chloride is added; the hydrochloride precipitates. The salt is crystallised from ethanol; its melting point is 170—172°C.

EXAMPLE 3

By using the procedure of Example 2 but substituting the 2 - [bis(*p* - fluorophenyl)-methoxy]ethyl chloride by the appropriate compounds of formula IV (with Hal=Cl) the following compounds of general formula II are obtained. The specified salts are prepared by addition of an ethereal solution of the appropriate acid to a solution of the base in diethyl ether.

(a) 2 - {[*p* - chloro - α - (*p* - fluorophenyl)benzyl]oxy}ethylamine, the hydrogen maleate of which melts at 134—136°C.;

(b) 2 - {[*o* - fluoro - α - (*p* - fluorophenyl)benzyl]oxy}ethylamine, the hydrochloride of which melts at 108—110°C.;

(c) 2 - {[*p* - bromo - α - (*p* - fluorophenyl)-benzyl]oxy}ethylamine, the hydrogen maleate of which melts at 133—135°C.;

(d) 2 - {[α - (*p* - bromophenyl)benzyl]-oxy}ethylamine, the hydrogen maleate of which melts at 134—135°C.;

(e) 2 - {[α - (*p* - fluorophenyl)benzoyl]-oxy}ethylamine, the hydrogen maleate of which melts at 130—132°C.;

(f) 2 - {[*p* - chloro - α - (*o* - fluorophenyl)-benzyl]oxy}ethylamine, the hydrogen maleate of which melts at 127—129°C., and

(g) 2 - {[α - (p - chlorophenyl)benzyl]-

oxy}ethylamine, the hydrochloride of which melts at 147—149°C.

The said salts of the ethers (a), (c) and (d) were crystallised from ethanol and diethyl ether, the salt of ether (b) was crystallised from methanol, diethyl ether and petroleum ether (boiling range 28—40°C.); the salt of ether (e) was crystallised from isopropanol and diethyl ether; the salt of ether (f) was crystallised from ethanol, diethyl ether and petroleum ether (boiling range 28—40°C.), and the salt of ether (g) was crystallised from ethanol, diethyl ether and petroleum ether (boiling range 40—60°C.).

EXAMPLE 4

A mixture of 5 g. (0.016 mole) of *N* - {2 - [bis(*p* - fluorophenyl)methoxy]ethyl}-acetamide and 4 g. (0.1 mole) of sodium hydroxide, dissolved in 25 ml. of ethanol, is refluxed for 17 hours. The reaction mixture is cooled and the ethanol is distilled off. The residue is taken up in water and extracted with diethyl ether. The extract is acidified with 2N hydrochloric acid, the aqueous layer is made alkaline with sodium hydroxide and extracted with diethyl ether. The extract is dried over potassium carbonate and the ether is distilled off. The residue is dissolved in diethyl ether and ethereal hydrogen chloride is added. The precipitate formed is crystallised from ethanol. 2 - [Bis(*p* - fluorophenyl)methoxy]ethylamine hydrochloride is obtained. Its melting point is 170—172°C.

The N - {2 - [bis(*p* - fluorophenyl)-methoxy]ethyl}acetamide, used as a starting material, is prepared as follows:

A mixture of 25.4 g. (0.1 mole) of bis(*p* - fluorophenyl)methyl chloride, 10.3 g. (0.1 mole) of *N* - (2 - hydroxyethyl)acetamide (prepared according to F. J. McQuillin *et al.*, J. Chem. Soc. *1955*, 2966), 14 g. of potassium carbonate and 100 ml. of benzene is refluxed for 5 hours. After cooling, the reaction mixture is poured into water. The aqueous layer is extracted with dichloromethane and the combined organic layers are dried over potassium carbonate and concentrated by evaporation of solvent. The residue is crystallised from toluene. *N* - {2 - [Bis(p - fluorophenyl)methoxy]ethyl}acetamide, m.p. 112—113.5°C., is obtained.

EXAMPLE 5

Using the procedure described in Example 4 but substituting an equivalent amount of *N* - {2 - [*o* - chloro - *α* - (*p* - fluorophenyl) benzyloxy]ethyl}acetamide for the *N* - {2 - [bis(*p* - fluorophenyl)methoxy]-ethyl}acetamide and maleic acid for the hydrogen chloride, there is obtained 2 - [*o* - chloro - *α* - (*p* - fluorophenyl)benzyloxy]-ethylamine hydrogen maleate, which is crystallised from ethanol. Its melting point is 123—123.5°C.

The amide starting material is prepared in the same way as described for the amide starting material in Example 4.

EXAMPLE 6

A solution of 1.2 g. (0.0043 mole) of 2 - [bis(*p* - fluorophenyl)methoxy]acetamide in 10 ml. of anhydrous tetrahydrofuran is added at room temperature to a suspension of 0.2 g. (0.0043 mole) of lithium aluminium hydride in 15 ml. of anhydrous tetrahydrofuran. The reaction mixture is refluxed for 3 hours. The mixture is then cooled, decomposed with water and extracted with diethyl ether. The ethereal phase is extracted with 0.5N hydrochloric acid; the extract is made alkaline again with sodium hydroxide and extracted with diethyl ether. The extract is dried over sodium sulphate and concentrated. A solution of maleic acid in diethyl ether is added and the precipitate, consisting of 2 - [bis(*p* - fluorophenyl)methoxy]ethylamine hydrogen maleate, is filtered off and crystallised from a mixture of methanol and diethyl ether. Its melting point is 126—127°C.

The amide starting material is prepared as follows:

23 g. (0.083 mole) of 2 - [bis(*p* - fluorophenyl)methoxy]acetic acid is shaken with 4.47 g. (0.083 mole) of sodium methoxide in 200 ml. of methanol. The methanol is distilled off and the residue, consisting of the sodium salt of 2 - [bis(*p* - fluorophenyl)-methoxy]acetic acid, is suspended in a small amount of dimethylsulphoxide, after which 38 g. of methyl iodide is added. The reaction mixture is kept standing for 17 hours at room temperature and then water is added. The mixture is extracted with diethyl ether. The extract is dried over sodium sulphate and the ether is distilled off. The residue, consists of 2 - [bis(*p* - fluorophenyl)methoxy]-acetic acid methyl ester. The product is dissoled in 200 ml. of methanol and a large excess of ammonia in methanol is added. The reaction mixture is kept standing for 18 hours at room temperture after which the solvent is distilled off. The solid residue is washed with a small amount of diethyl ether and twice crystallized from toluene. 2 - [Bis(*p* - fluorophenyl)methoxy]acetamide is obtained. Its melting point is 110—111.5°C.

EXAMPLE 7

A solution of 7.5 g. (0.027 mole) of 2 - [bis(*p* - fluorophenyl)methoxy]acetonitrile in 10 ml. of anhydrous tetrahydrofuran is added drop-wise at room temperature to a suspension of 1 g. (0.027 mole) of lithium aluminium hydride in 60 ml. of anhydrous tetrahydrofuran. The reaction mixture is refluxed for 8 hours and is then decomposed and further treated as described in Example

6. 2 - [Bis(*p* - fluorophenyl)methoxy]ethylamine hydrogen maleate, melting point 126—127°C., is obtained.

The nitrile starting material is prepared as follows:

A mixture of 20 g. (0.14 mole) of phosphorus pentoxide and 15 g. of calcinated diatomaceous earth (trade-mark "Hyflo") in 100 ml. of anhydrous toluene is added dropwise to a stirred and refluxing mixture of 14 g. (0.05 mole) of 2 - [bis(*p* - fluorophenyl)methoxy]acetamide, 70 ml. of toluene and 34 ml. of triethylamine (dried over phosphorus pentoxide). The reaction mixture obtained is refluxed for 30 minutes, cooled and shaken with an aqueous sodium chloride solution. The organic phase is dried and concentrated and the oily residue is distilled. The boiling point of the obtained nitrile is 138—145°C./0.65 mm.Hg.

The invention includes within its scope pharmaceutical compositions comprising, as active ingredient, at least one of the therapeutically active ethers of formula II, or a non-toxic acid addition salt thereof, in association with a pharmaceutically-acceptable carrier.

The preparations may take any of the forms customarily employed for administration of therapeutic substances. Tablets and pills may be formulated in the usual manner with one or more pharmaceutically acceptable diluents or excipients, for example lactose or starch, and include materials of a lubricating nature, for example calcium or magnesium stearate. Capsules made of absorbable material, such as gelatin, may contain the active substance alone or in admixture with a solid or liquid diluent. Liquid preparations may be in the form of suspensions, emulsions, syrups or elixirs of the active substance in water or other liquid medium commonly used for making orally acceptable pharmaceutical formulations, such as liquid paraffin, or a syrup or elixir base. The active substance may also be made up in a form suitable for parenteral administration, i.e. as a suspension or emulsion in sterile water or an organic liquid usually employed for injectable preparations, for example a vegetable oil such as olive oil, or a sterile solution in water or an organic solvent.

The following Example illustrates pharmaceutical compositions according to the invention.

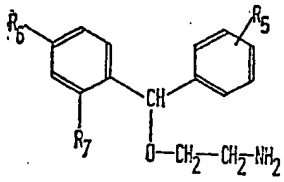
EXAMPLE 8

50 g. of 2 - [bis(*p* - fluorophenyl)-methoxy]ethylamine hydrochloride, 33 g. of saccharis lactis, 87 g. of amylum and 10 g. of polyvinylpyrrolidone, are mixed and granulated with ethanol. The granulate is dried and mixed with 14 g. of amylum and 6 g. of a mixture of 8 parts of talcum, 1 part of Aerosil (a Registered Trade Mark) and 1 part of magnesium stearate. The mixture is then compressed into tablets of 200 mg., each containing 50 mg. of the active substance.

As mentioned at the beginning of the specification, 2 - {[α - (*p* - chlorophenyl)-benzyl]oxy}ethylamine is a known compound. It has previously been associated with diethyl ether, and its hydrochloride has been associated with a mixture of ethanol and diethyl ether. It is to be understood that diethyl ether, and mixtures of ethanol and diethyl ether, are not suitable pharmaceutically-acceptable carriers for the aforesaid compound of other compounds of general formula II, or acid addition salts thereof.

WHAT WE CLAIM IS:—

1. Diphenylmethoxyethylamines of the general formula:



in which R_5 represents a fluorine, bromine or chlorine atom, R_6 represents a hydrogen or fluorine atom and R_7 represents a hydrogen, fluorine or chlorine atom, with the provisos that R_7 is a hydrogen atom when R_6 is a fluorine atom, R_5 is a fluorine atom when R_7 is a chlorine atom, and R_5 is a fluorine or bromine atom when R_6 and R_7 are hydrogen atoms, and acid addition salts thereof.

2. Diphenylmethoxyethylamines according to claim 1 in which R_5 represents a fluorine or chlorine atom, and R_6 or R_7 represents a fluorine atom.

3. 2 - [Bis(*p* - fluorophenyl)methoxy]-ethylamine and acid addition salts thereof.

4. 2 - {[*p* - Chloro - α - (*p* - fluorophenyl)benzyl]oxy}ethylamine and acid addition salts thereof.

5. 2 - {[*o* - Fluoro - α - (*p* - fluorobenzyl)-benzyl]oxy}ethylamine and acid addition salts thereof.

6. 2 - {[*p* - Bromo - α - (*p* - fluorophenyl)benzyl]oxy}ethylamine and acid addition salts thereof.

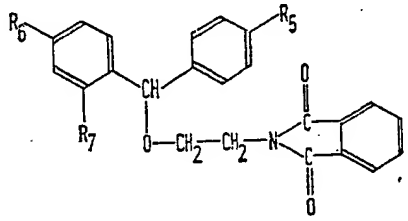
7. 2 - {[α - (*p* - Bromophenyl)benzyl]-oxy}ethylamine and acid addition salts thereof.

8. 2 - {[α - (*p* - Fluorophenyl)benzyl]-oxy}ethylamine and acid addition salts thereof.

9. 2 - {[*p* - Chloro - α - (*o* - fluorophenyl)benzyloxy} - ethylamine and acid addition salts thereof.

10. 2 - {[*o* - Chloro - α - (*p* - fluorophenyl)benzyl]oxy}ethylamine and acid addition salts threeof.

11. Process for the preparation of diphenylmethoxyethylamines as claimed in claim 1 which comprises removing by a method known *per se* the phthaloyl group of a phthalimide derivative of the general formula:



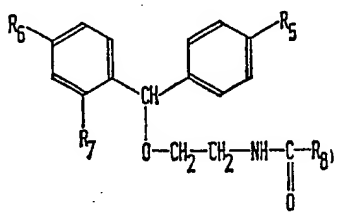
in which R_5, R_6 and R_7 are as defined in claim 1.

12. Process according to claim 11 in which the phthalimide derivative is reacted with hydroxylamine or an acid addition salt thereof.

13. Process according to claim 12 in which the reaction is carried out at room temperature.

14. Process according to claim 12 or 13 in which the reaction is carried out in the presence of an alkoxide dissolved in a lower alcohol.

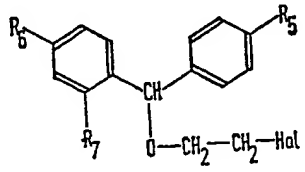
15. Process for the preparation of diphenylmethoxyethylamines as claimed in claim 1 which comprises hydrolyzing an amide of the general formula:



in which R_5, R_6 and R_7 are as defined in claim 1 and R_8 represents a hydrogen atom or an alkyl, aryl or aralkyl group, said groups containing at most 10 carbon atoms.

16. Process according to claim 15 in which hydrolysis of the amide is carried out by refluxing the amide in a lower alcohol in the presence of a base.

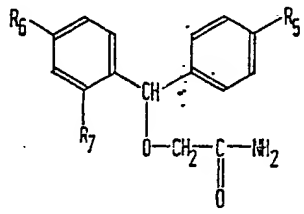
17. Process for the preparation of diphenylmethoxyethylamines as claimed in claim 1 which comprises reacting an ether of the general formula:



in which R_5, R_6 and R_7 are as defined in claim 1 and Hal represents a halogen atom, with ammonia.

18. Process according to claim 17 in which the ether, dissolved in a lower alcohol, is heated with a large excess of ammonia in a closed vessel.

19. Process for the preparation of diphenylmethoxyethylamines as claimed in claim 1 which comprises reducing by a method known *per se* as amide of the general formula:

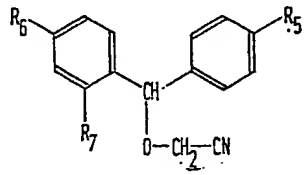


in which R_5, R_6 and R_7 are as defined in claim 1.

20. Process according to claim 19 in which reduction of the amide is effected with lithium aluminium hydride, followed by decomposition of the complex compound obtained with water.

21. Process according to claim 20 in which the reaction with lithium aluminium hydride is carried out in diethyl ether or tetrahydrofuran.

22. Process for the preparation of diphenylmethoxyethylamines as claimed in claim 1, which comprises reducing a nitrile of the general formula:



in which R_5, R_6 and R_7 are as defined in claim 1, by a method known *per se* for the reduction of a nitrile to a primary amine.

23. Process according to claim 22 in which the reduction is effected by reaction of the nitrile with lithium aluminium hydride, followed by decomposition of the complex obtained with water.

24. Process according to claim 23 in which the reaction with lithium aluminium hydride is carried out in diethyl ether or tetrahydrofuran.

25. Process according to any one of claims 11 to 24 followed by the step of converting a diphenylmethoxyethylamine base obtained into an acid addition salt.

26. Process for the preparation of diphenylmethoxyethylamines of the general formula specified in claim 1 and acid addition salts thereof substantially as described in any one of Examples 1 to 7.

27. Diphenylmethoxyethylamines of the general formula specified in claim 1 and acid addition salts thereof when prepared by the process claimed in any one of claims 11 to 26.

28. Pharmaceutical compositions which comprise, as active ingredient, at least one diphenylmethoxyethylamine as claimed in any one of claims 1 to 10, or a non-toxic acid addition salt thereof, in association with a pharmaceutically-acceptable carrier.

29. Pharmaceutical compositions which comprise, as active ingredient, 2 - {[α - (*p* - chlorophenyl)benzyl]oxy}ethylamine, or a non-toxic acid addition salt thereof, in association with a pharmaceutically-acceptable carrier.

30. Pharmaceutical compositions according to claim 28 or 29 substantially as hereinbefore described with especial reference to Example 8.

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